Pharmacological approach to rapid sequence induction/intubation: a contemporary perspective

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Purpose of review:
This review examines the evolution of the pharmacological approach to rapid sequence induction/intubation (RSII) over the past 55 years, highlighting recent advances and contemporary perspectives on managing full-stomach patients requiring airway control.

Recent findings:
While aspiration remains a significant concern during RSII (occurring in 3–6% of cases), recent data suggests that desaturation, hypoxemia, and hemodynamic instability pose even greater risks, particularly in critically ill patients. Modern RSII approaches have evolved significantly from Safar's original protocol. Cricoid pressure is increasingly questioned, with evidence suggesting it may be unnecessary except when active regurgitation is observed. Gentle ventilation postinduction appears safe and beneficial when desaturation risk is high. Regarding pharmacology, succinylcholine has largely been replaced by rocuronium, while ketamine and etomidate are preferred over propofol for hemodynamically unstable patients. glucagon-like peptide 1 agonists may increase residual gastric content but have not definitively been linked to increased aspiration rates. First-pass success (currently ~84%) is crucial, as complications increase exponentially with multiple attempts.

Summary:
Contemporary RSII should balance aspiration prevention with avoiding hypoxemia and hemodynamic collapse. This requires thorough patient assessment, appropriate drug selection, optimal positioning, and effective teamwork. The priority should be making the first intubation attempt the best possible attempt, with preintubation optimization and consideration of human factors.

Keywords
airway management, aspiration prevention, critical care intubation, hemodynamic stability, rapid sequence induction

INTRODUCTION

The management of a full-stomach patient presents a significant challenge for airway control, requiring meticulous planning and careful selection of medications, patient positioning, devices, and timing of maneuvers. This complexity is already reflected in the original definition of rapid sequence induction (RSII), as proposed by Stept and Safar in their landmark 1970 paper [1]. Throughout this text, we will refer to the technique as RSII, aiming to highlight the core principles of this essential procedure in light of the advancements made over the past 55 years. For decades, the primary concern during anesthetic induction in full-stomach patients has been regurgitation and subsequent aspiration of gastric contents – a risk recognized even before Stept and Safar's publication, as evidenced by Sellick's work advocating the application of cricoid pressure as a life-saving maneuver during induction [2]. Since then, many concepts and practices have evolved. This review aims to examine these developments and provide updated insights into the modern approach to RSII.

IS ASPIRATION STILL OUR GREATEST CONCERN?

Several studies have explored the incidence of aspiration in high-risk, full-stomach patients [3],

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KEY POINTS

- While aspiration remains a significant concern during rapid sequence induction/intubation (RSII) (3–6% of cases), recent evidence suggests that desaturation and hemodynamic instability represent even greater risks, particularly in critically ill patients.
- Modern RSII has evolved significantly from its original formulation, with cricoid pressure now questioned, gentle ventilation considered beneficial in high-risk patients, and a shift from succinylcholine to rocuronium for neuromuscular blockade.
- Optimal drug selection is crucial during RSII, with ketamine and etomidate preferred over propofol for hemodynamically unstable patients, though definitive evidence favoring one agent over another remains limited.
- First-pass intubation success (currently ~84%) should be prioritized through proper preparation, effective preoxygenation, appropriate device selection, and consideration of human factors.
- A contemporary approach to RSII requires balancing aspiration prevention with avoiding oxygen desaturation and cardiovascular collapse through individualized risk assessment and tailored management strategies.

starting with Mendelson's landmark paper in 1946 [4]. A 1993 study reported that pulmonary aspiration complicated between 1 in 900 and 1 in 10 000 general anesthetics, offering a wide range of incidence [5]. The 2011 National Audit Project 4 (NAP4), a cornerstone in airway management research, found that more than 50% of anesthesia-related deaths involved aspiration [6]. Aspiration was the primary or secondary event in 23% of all cases, correlating with increased morbidity and prolonged hospital stay. NAP4 estimated the incidence of aspiration at 1 in 350 000 anesthetic cases – lower than earlier estimates (1 in 45 000 and 1 in 240 000) – but still identifying it as the leading cause of airway-related mortality (50% of anesthetic deaths and 17% of reported primary anesthesia events), particularly in emergency and ICU settings [6]. The webAIRS database, a web-based reporting system from Australia and New Zealand, recorded aspiration in 121 of 4000 anesthesia-related incidents (3%) [7]. More recently, NAP7, surveying 24 721 cases, reported an aspiration incidence of 6% [8]. However, the most common respiratory complications were severe difficult ventilation (37%) and hypoxemia (23%). Data from the ASA Closed Claims Project documented 115 cases of aspiration among 2496 claims (5%) [9]. More than half of these cases resulted in death, while an additional third caused permanent severe injury. Aspiration was often associated with gastrointestinal obstruction or acute intra-abdominal pathology requiring emergency intubation. Notably, substandard anesthetic care was identified in almost 60% of these claims. The Intubation Practices and Adverse Peri-intubation Events (INTUBE) study, encompassing 2964 critically ill patients from 197 ICUs worldwide, found that RSII was performed in only 62% of cases, with cricoid pressure applied in 38%. Aspiration occurred in 3.9% of patients [10▪]. In summary, aspiration occurs in approximately 3–6% of anesthetic inductions, predominantly during emergency procedures involving intestinal obstruction or intra-abdominal diseases, especially in emergency department and ICU settings. Interestingly, in emergency and ICU intubations, the incidence of aspiration remains lower than that of desaturation and hypoxemia, and significantly lower than hemodynamic instability (9.3 and 42.6%, respectively, in the INTUBE study), including intubation-associated cardiac arrest. Thus, 55 years later, while we still fear aspiration, critical data suggest that desaturation and cardiovascular instability are even more frequent and dangerous in critically ill patients. It may be time to reconsider and modernize our approach to RSII.

PROACTIVE VERSUS REACTIVE APPROACH DURING RSII

A modern approach to RSII should include a thorough evaluation of the patient, assessing not only the risk factors for aspiration but also for desaturation and hemodynamic instability – without neglecting airway management evaluation. According to recent European Society of Anaesthesiology and Intensive Care guidelines [11], airway assessment should be context-sensitive, considering not only anatomical predictors but also physiological difficulties (including aspiration risk) [12], the availability of devices, the environment, and the expertise of both the airway manager and the team [11]. Aspiration risk factors are well-established (Table 1), and prevention remains a key strategy to mitigate gastric content regurgitation.

Any local or systemic disease delaying gastric emptying, especially gastrointestinal obstruction, should be considered a significant aspiration risk.

Recent literature has also raised concerns about glucagon-like peptide 1 (GLP-1) agonists:

- A study in *JAMA* found that GLP-1 receptor agonists were associated with increased residual

Table 1 Aspiration risk factors

Team	Patient	Devices	History	Anesthesia
Airway manager expertise	Inadequate fasting	Supraglottic airway devices (>1st gen)	Emergency induction	Positive pressure ventilation
Team expertise	Use of GLP-1 agonists (?) [50]	Face mask	Gastrointestinal obstruction	Light anesthesia
Airway plan	Diabetes (DGE)	Classic direct laryngoscopy	Previous gastrointestinal surgery	Difficult airway
	Chronic kidney disease		Lithotomy/head down position	Repeated intubation attempts
	Trauma		Laparoscopy	Choice of medications
	Use of opioids (DGE)		Critically ill patients	
	Pregnancy		Hyatal hernia, reflux disease	
	Hyatal hernia			
	Raised intracranial pressure			
	Morbid obesity			
	Coma			
	Hemodynamic instability			

DGE, delayed gastric emptying; GLP-1, glucagon-like peptide 1.

gastric content on preprocedural ultrasound, suggesting the need to reconsider fasting guidelines [13].

- Conversely, another cohort study in *JAMA* reported no significant association between GLP-1 use and short-term postoperative aspiration pneumonia, despite increasing concerns [14].
- A recent meta-analysis supported these findings, showing increased residual gastric content without a corresponding increase in pulmonary aspiration rates [15].

Gastric ultrasound has recently been proposed as a tool to evaluate both the quantity and quality of gastric contents, potentially guiding decisions to delay induction or adopt alternative strategies to minimize aspiration risk [16]. Preemptive nasogastric tube placement, as originally suggested by Safar and later discussed, remains controversial, as it may fail to drain semisolid content and could impair lower esophageal sphincter function [17]. Two recent worldwide surveys highlighted extreme variability in techniques and strategies used to prevent aspiration, underlining the urgent need for more evidence-based recommendations rather than reliance on empirical habits [18,19]. Regarding patient positioning during RSII, evidence remains controversial. The once-standard use of cricoid pressure (Sellick's maneuver) has been widely questioned [20], notably by Birenbaum's pivotal study, which significantly debunked its efficacy [21▪▪]. Current perspectives, including the forthcoming PUMA guidelines, suggest applying cricoid pressure only if regurgitation is witnessed during induction [22]. Otherwise, its routine use is likely to be abandoned soon. Another major evolution in RSII practice concerns ventilation after anesthetic induction. Originally, Sellick and Safar recommended withholding ventilation after preoxygenation. However, recent evidence, including the study by Casey *et al.* [23▪▪], suggests that gentle ventilation (15–17 cm H_2O) postinduction can be safe and beneficial – especially when hypoxia or hemodynamic collapse is the primary concern – thus reaffirming concepts already hinted at in 1987 [24].

PHARMACOLOGY OF RSII

Many years after Safar's pioneering work, there is still no full consensus on RSII [25], and this lack of agreement becomes even more evident when considering the drugs used for induction [26].

Historically, Safar's original triad involved the following:

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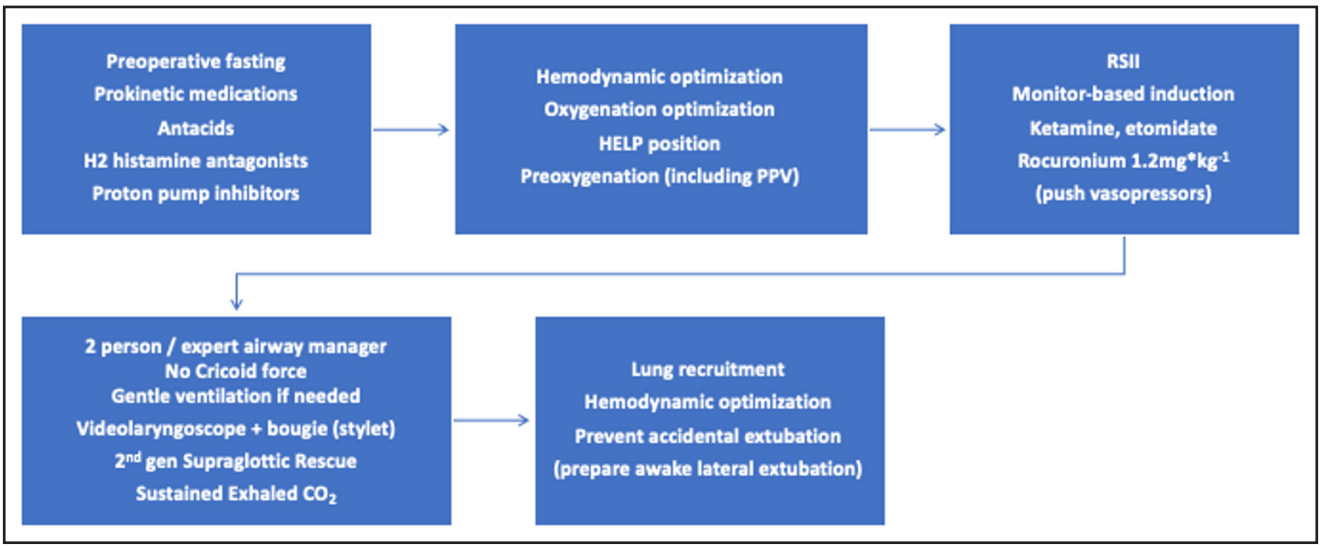

FIGURE 1 Modified rapid sequence induction/intubation in 2025. RSII, rapid sequence induction/intubation.

- Priming with d-tubocurarine 3 mg/70 kg ('…to produce a slight weakness, but most of patients won't notice…')
- Induction with thiopental 150 mg/70 kg, which could be omitted in comatose patients or replaced with scopolamine, cyclopropane, or halothane in conscious, hemodynamically unstable patients ('…the conscious patient whose circulation may not tolerate thiopental, until the eyelash reflex is sluggish…')
- Neuromuscular blockade with succinylcholine chloride (100 mg/70 kg), administered immediately after unconsciousness, maintaining apnea until laryngoscopy and intubation.

Today, priming with neuromuscular blocking agents is no longer recommended, and succinylcholine has been largely replaced by rocuronium (1.2 mg/kg) [27]. Notably, Safar had already emphasized the importance of neuromuscular monitoring, which remains critical in modern RSII. Some of Safar's intuitions have been validated by later data: a subanalysis of the INTUBE study found that propofol (the modern evolution of thiopental) was independently associated with hemodynamic collapse during RSII in critically ill patients (odds ratio: 1.23), regardless of preintubation blood pressure [28▪].

WHICH AGENTS SHOULD BE USED FOR RSII, ESPECIALLY IN CRITICALLY ILL PATIENTS?

This is a crucial question, as drug choice impacts not only hemodynamics but also the risk of desaturation, hypoxemia, and aspiration. An inadequate anesthetic plan can itself trigger gastric regurgitation. However, when dealing with hemodynamically unstable patients, there is often a temptation to use lower, subtherapeutic doses of induction and neuromuscular blocking agents – an approach that should be avoided. Induction agents should be given at full doses, calculated based on the patient's actual, ideal, or adjusted body weight as appropriate, ideally guided by anesthetic depth monitoring. A recent Delphi consensus on airway management in critically ill patients recommends avoiding propofol for RSII, instead favoring etomidate and ketamine [29]. Historical concerns regarding ketamine and elevated intracranial pressure, as well as about etomidate's effect on adrenal function after a single dose, have largely been dismissed. However, there are no clear criteria favoring one over the other, and further research is needed [30–32]. Some studies suggest a safer hemodynamic profile for ketamine, but larger trials are necessary before definitive recommendations can be made [33,34]. Coinduction agents such as midazolam or remimazolam [35] may be considered, and new induction agents (e.g. ciprofol, esketamine, and ketofol) are under investigation to optimize the balance between hypnosis and hemodynamic stability. Hemodynamic optimization is also an integral part of RSII pharmacology:

- Preemptive or 'push-dose' administration of vasoactive agents and fluids has been explored, but evidence remains limited [36▪].
- Empirical fluid boluses before intubation are not universally recommended and should

instead be based on individualized assessment of fluid status and responsiveness [37].
- Similarly, vasopressor use is debated: although it may prevent hypotension, it could theoretically worsen oxygen debt during a critical phase. Thus, tailored administration, guided by advanced hemodynamic monitoring, is the preferred future direction, pending results from ongoing studies [38,39].

Finally, a further pharmacological strategy is to avoid induction drugs altogether, opting for awake intubation in a spontaneously breathing, preoxygenated, and lightly sedated patient [40▪,41]. This approach is supported by several airway management guidelines, especially when RSII is indicated in the context of a predicted difficult airway.

FIRST-PASS SUCCESS AND HUMAN FACTORS IN RSII

As with aspiration risk, prevention remains the most effective strategy to reduce the incidence of hypoxemia and hemodynamic collapse during RSII. Whenever possible, intubation should be postponed – or better, planned in advance – to allow for optimal patient preparation, including proper preoxygenation (potentially enhanced by noninvasive ventilation) [42], hemodynamic optimization before induction. A modern, modified RSII should, therefore, include preintubation optimization, effective preoxygenation, extending into apneic oxygenation during airway manipulation [43], and gentle ventilation ('gentilation') if needed, to avoid desaturation without increasing aspiration risk. The first intubation attempt must be the best attempt, since the incidence of complications increases exponentially with the number of attempts [44▪]. In the context of critically ill patients, a modern RSII approach should prioritize the use of a videolaryngoscope in combination with a bougie or stylet, ensuring careful confirmation of tube position [45], and immediate postintubation optimization of the patient's respiratory and hemodynamic status (Fig. 1).

CONCLUSION: HUMAN FACTORS AND THEIR IMPACT ON RSII

Human factors are increasingly recognized as pivotal contributors to adverse events during RSII, as highlighted by data from the NAP4 report [6], the INTUBE study [10▪▪], and various simulation-based investigations [46]. RSII has to be played as a team effort, with clear role definitions, well-established preprocedural planning and backup strategies, and hopefully sustained by checklists, cognitive supports, and a favorable ergonomics [28▪,47]. In this context, 'rapid' should be interpreted as efficient yet deliberate. More than in routine airway management, RSII requires anticipation, preparation, and structured execution. Despite advancements in airway management, the current first-pass success rate during RSII remains approximately 84%, underscoring the need for further improvement [48]. While appropriate device and pharmacologic choices are fundamental determinants of procedural success and complication rates, there is growing consensus that optimizing human factors – through enhanced teamwork, preparation, and cognitive readiness – represents the most impactful avenue to improve patient safety and outcomes during RSII.

As Wolfgang Pauli famously stated:

'I do not mind you intubating quickly, just not faster than you can think' [49].

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Conflicts of interest

None with this study. M.S. has received paid consultancy from Teleflex Medical, Verathon Medical, and DEAS Italia; he is a patent co-owner (no royalties) of DEAS Italia and has received lecture grants and travel reimbursements from MSD Italia and Boston Scientific France, Flexicare Italy. M.S. and L.L.V. have NDA with Flexicare Italy and AI Endoscopic, Zurich. For the remaining author, there are no conflicts of interest.

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